California Institute for Regenerative Medicine

Cdc37 regulates Ryk signaling by stabilizing the cleaved Ryk intracellular domain.

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Public Summary:

Scientific Abstract:
Ryk is a Wnt receptor that plays an important role in neurogenesis, neurite outgrowth, and axon guidance. We have reported that the Ryk receptor is cleaved by gamma-secretase and that its intracellular domain (ICD) translocates to the nucleus upon Wnt stimulation. Cleavage of Ryk and its ICD is important for the function of Ryk in neurogenesis. However, the question of how the Ryk ICD is stabilized and translocated into the nucleus remains unanswered. Here, we show that the Ryk ICD undergoes ubiquitination and proteasomal degradation. We have identified Cdc37, a subunit of the molecular chaperone Hsp90 complex, as a Ryk ICD-interacting protein that inhibits proteasomal degradation of the Ryk ICD. Overexpression of Cdc37 increases Ryk ICD levels and promotes its nuclear localization, whereas Cdc37 knockdown reduces Ryk ICD stability. Furthermore, we have discovered that the Cdc37-Ryk ICD complex is disrupted during neural differentiation of embryonic stem cells, resulting in Ryk ICD degradation. These results suggest that Cdc37 plays an essential role in regulating Ryk ICD stability and therefore in Ryk-mediated signal transduction.

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